Remarks

Claims 7-9, 11-15, 17, 21 and 43-50 were pending. Due to the restriction requirement, claim 47 is cancelled without prejudice to prosecution in a future application. No claims were added. Therefore, claims 7-9, 11-15, 17, 21, 43-46 and 48-50 are now pending.

Applicant thanks the examiner for withdrawing all of the previous rejections.

Allowable subject matter

There appears to be no rejection of claims 9, 14, 44, 45, 46, and 49 in the outstanding Office action. However, there is no mention in the Office action that these claims are allowable, for example if written in independent form. Applicant requests confirmation that at least claims 9, 14, 44, 45, 46, and 49 are directed to allowable subject matter.

35 U.S.C. § 102(a)

Claims 7, 11, and 15 are rejected under 35 U.S.C. § 102(a) as anticipated by Arya *et al.* (*Human Gene Therapy,* 9:1371-80, 1998). Applicant disagrees and requests reconsideration.

Enclosed is a Rule 132 Declaration signed by inventor Arya stating that the Arya *et al.* publication is the work of Dr. Arya and that the co-authors (Zamani and Kundra) are not inventors.

Therefore, the 35 U.S.C. § 102(a) rejection is overcome, and Applicant requests that it be withdrawn.

35 U.S.C. § 103(a)

Claims 7, 8, 11-13, 15, 17, 21, 43, 48 and 50 are rejected under 35 U.S.C. § 103(a) as unpatentable over Arya *et al.* and Verma *et al.* (US Patent No. 6,013,516). Applicant disagrees and requests reconsideration.

As noted above, Arya *et al.* is not prior art to the present application. Therefore, it cannot be combined with Verma *et al.* in an obviousness rejection. Therefore, this 35 U.S.C. § 103(a) rejection is improper, and Applicant requests that it be withdrawn.

Claims 7, 8, 11-13, 15, 17, 21, 43, 48 and 50 are rejected under 35 U.S.C. § 103(a), as unpatentable over McCann *et al.* (*J. Virol.* 71:4133-7, 1997) and Verma *et al.* (US Patent No. 6,013,516). It is concluded on page 6 of the Office action that one of ordinary skill in the art at the time of invention would have been motivated to combine the mutations of McCann and Lever to create a vector with deletions both upstream and downstream knowing that mutations upstream and downstream of the SD site were involved in packaging with the expectation of reducing packaging even further. Applicant disagrees and requests reconsideration.

McCann and Lever only teach functional deletion of an HIV-2 packaging signal by deletions upstream *or* downstream of the SD site. Each of the four deletions made by McCann and Lever (shown as Δ1, Δ2, Δ3, and Δ4 in FIG. 1 of McCann and Lever) were made *individually, not in combination*. As stated on page 4133 (first column, 3rd paragraph) of McCann and Lever, "...four deletion mutations were introduced into the 5' UTR of HIV-2, removing sequences immediate upstream or downstream of the 5' major splice donor..." (emphasis added). Therefore, McCann and Lever do not teach a deletion of *both* signals upstream *and* downstream of the SD site. In contrast, the claims of the present invention are directed to an HIV-2 packaging vector that includes functional deletions of the upstream and downstream packaging signal sequences.

There is no teaching or suggestion in McCann and Lever (or Verma *et al.*) that deletions of both upstream and downstream packaging signal sequences (such as combining Δ 1 or Δ2 with Δ3 or Δ4 in FIG. 1 of McCann and Lever) will further reduce packaging of progeny viral RNA. In fact, McCann and Lever repeatedly teach away from the present invention, by disclosing that the role of the region deleted by Δ3 and Δ4 makes only a minor contribution to packaging. For example, page 4135 (first column, first full paragraph) states "deletions between the splice donor and the *gag* gene of HIV-2 [the region deleted by Δ3 and Δ4] make only a minor contribution to packaging and cause no replication defect." In addition, page 4134 (column 1, lines 6-11) states "...the Δ 3 and Δ4 mutants both package genomic RNA at approximately 50% of the [HIV-2] wild type level. The scale of the packaging defect for these two mutants is modest compared to that reported for analogous HIV-1 mutants, which typically show a 10- to 100-fold encapsidation defect...." Instead, McCann and Lever teach that the region covered by Δ2 is important for packaging (see page 4135, second column, first sentence). Therefore, the

McCann and Lever document teaches that the region covered by Δ3 and Δ4 (downstream sequence element) makes only a minor or no contribution to RNA encapsidation, while the major element (Δ2) is upstream of the splice donor site. Therefore, one skilled in the art would not be motivated to combine deletions upstream and downstream of the splice donor site, since McCann and Lever teach that the downstream region only provides a minor, if any, contribution to packaging.

The data presented in the present application demonstrates an unexpectedly superior result over McCann and Lever. It is shown in the present application that deletions made both upstream and downstream of the splice donor site provided enhanced reduction in packaging, as compared to either deletion alone. For example, as shown in FIG. 9 (also described on page 33, lines 1-12), HIV-2 vectors containing deletions upstream (SK36) or downstream (PK36) reduce viral RNA packaging, with deletions upstream reducing packaging by a greater amount. However, deletion of sequences both upstream and downstream of the splice donor site (SD36) demonstrates an enhanced unexpected reduction in viral RNA packaging, a reduction of more than 80%, such as 90-95%. This observed effect is more than additive. Such significant packaging reduction would not have been expected by combining the two deletions, especially since McCann and Lever teach that this region only modestly reduces viral RNA packaging.

Because the disclosure of McCann and Lever teach away from the present invention, and because the present invention provides an unexpectedly superior result over McCann and Lever, this 35 U.S.C. § 103(a) rejection is improper, and Applicant requests that it be withdrawn.

If there are any minor issues to be resolved before a Notice of Allowance is granted, the examiner is invited to telephone the undersigned.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By _____
Sheree Lynn Rybak, Ph.D.
Registration No. 47,913